in the specification, with deletions and additions indicated by brackets and underlining, respectively, is attached hereto as Exhibit A. The amendments to the specification do not constitute new matter.

Claims 1-21 were pending in this application. Applicants have canceled claims 10, 11, and 18-21, without prejudice to Applicants' right to pursue the subject matter of the canceled claims in related applications. Applicants have amended claim 7 and 12-17 and added new claims 22-33, directed to methods of inducing both cytoprotective and NF-κB inhibitory activities in a human comprising administering to a human in which such treatment is desired a therapeutically effective amount of a compound with a cyclopentenone ring structure that induces the expression of one or more heat shock proteins and downregulates or inhibits NF-κB activity. Claim 7 has been amended merely to make grammatical changes. The amendments to the claims in no way narrow the scope of the claims. A marked up version of the claims amended herein, with deletions and additions indicated by brackets and underlining, respectively, is attached hereto as Exhibit B. Support in the specification for the amendments and new claims can be found throughout, for example at page 4, line 35 to page 5, line 8, page 9, lines 24-34, page 10, lines 14-33, page 11, line 10 to page 12, line 32, and page 13, line 1 to page 17, line 12 of the instant specification. Thus, Applicants assert that the amendments and new claims do not constitute new matter. Upon entry of this amendment, claims 1-9 and 12-17 and 22-33 will be pending in the instant application. A copy of the pending claims is attached hereto as Exhibit C.

RESPONSE TO RESTRICTION REQUIREMENT

The Examiner has required an election under 35 U.S.C. § 121 of one of the following groups:

I. Claims 1, 2, and 8, drawn to a method for treating various viral etiological agents by administering various cyclopentenone compounds;

II. Claims 3 and 8, drawn to a method for treating inflammation by administering various cyclopentenone compounds;

III. Claims 4 and 8, drawn to a method for treating cancer by administering various cyclopentenone compounds;

IV. Claims 5 and 7-17, drawn to a method for inducing cytoprotective responses by administering various cyclopentenone compounds;

V. Claims 6-17, drawn to a method for inhibiting NF-κB activation by administering various cyclopentenone compounds;

VI. Claims 18 and 21, drawn to a method for treating various viral etiological agents by administering compounds that induce heat shock protein, or inhibit NF-κB activation;

VII. Claims 19 and 21, drawn to a method for treating inflammation by administering compounds that induce heat shock protein, or inhibit NF-κB activation; and

VIII. Claims 20 and 21, drawn to a method for treating cancer by administering compounds that induce heat shock protein, or inhibit NF-κB activation.

In addition, the Examiner has required an election of a species. In particular, the Examiner has required that upon the election of a group, a single therapeutic regimen and a single compound be elected for examination as species.

Applicants respectfully submit that to search and examine the subject matter of Groups I-V together would not be a serious burden on the Examiner. The M.P.E.P. § 803 (Eighth Edition, August 2001) states:

> If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions.

Thus, in view of M.P.E.P. § 803, the claims of Groups I-V should be searched and examined in the subject application. Accordingly, Applicants respectfully request that the Restriction Requirement Under 35 U.S.C. § 121 be modified such that the subject matter of the claims of Groups I-V, claims 1-9, 12-17 and 22-33, are examined in the subject application.

Further, Applicants note that Groups IV and V differ only by a single claim, *i.e.*, both groups include claims 7-17. Indeed, claim 7 unites the methods of claims 5 and 6. Therefore, Applicants respectfully request, at a minium, modification of the restriction such that Groups IV and V are examined together. In other words, upon election of Group IV, Applicants respectfully request that the Examiner consider and exam claim 6 from Group V.

In order to be fully responsive, Applicants hereby provisionally elect, with traverse, to prosecute the subject matter of the claims of Group IV, claims 5, 7-17 and 22-33. As species, Applicants hereby provisionally elect, with traverse, to prosecute a method for inducing both

cytoprotective and NF-κB inhibitory activities in a human infected with a virus as the method and 2-cyclopenten-1-one as the compound.

Entry of the amendments and remarks made herein into the file of the above-identified application is respectfully requested. The Examiner is invited to contact the undersigned with any questions concerning the foregoing.

It is estimated that no amendment fee is necessary for filing this response. In the event an additional fee is required, please charge the required fee to Pennie & Edmonds Deposit Account No. 11-1650.

Respectfully submitted,

Date December 14, 2001

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Enclosures

EXHIBIT A

A MARKED UP VERSION OF THE AMENDED PARAGRAPHS

IN THE SPECIFICATION OF U.S. APPLICATION SERIAL NO.: 09/533,399

ATTORNEY DOCKET NO. 10167-004

(DECEMBER 14, 2001)

On page 2, please amend the paragraph beginning on line 5 as follows:

One successful approach in combating viral infections appears to be the simultaneous use of two or more drugs that affect different targets during the virus life cycle. A group of prostaglandins (PG) and PG-derivatives containing an α,β,- unsaturated carbonyl group in the cyclopentane ring (cyclopentenone PG, cyPG) have been shown *in vitro* to have the interesting ability to interfere with virus replication at multiple [level] levels (Santoro et al., 1997, Trends Microbiol. 5: 276-281). For example, prostaglandins of the A and J type (PGAs and PGJs) have been shown to inhibit the replication of a variety of RNA viruses, including paramyxoviruses, rhabdoviruses, rotaviruses and retroviruses in cultured cells (reviewed in Santoro et al., 1997, *supra*).

On page 3, please amend the paragraph beginning on line 13 as follows:

The inactive form of NF-κB is localized in the cytoplasm, and upon activation by a variety of agents (*e.g.*, cytokines, oxygen free radicals, inhaled particles, ultraviolet light, bacterial products, and viral products) is translocated to the nucleus. NF-κB is tightly associated with a class of specific inhibitory proteins, called IκBs, that prevent the translocation and DNA binding of the transcription factor (see, *e.g.*, Chen et al., 1999, Clinical Chemistry 45:7-17 and Baeuerle, 1998, Cell 95:729-731). In response to a variety of agents, IκB is phosphorylated in its N-terminal domain by a large multikinase complex, polyubiquitinylated, and degraded by the proteasome (see, *e.g.*, Baeuerle, 1998, Curr. Biol. 8:R19-R22; Ghosh et al., 1998, Annu. Rev. Immunol. 16:225-260). Once NF-κB is dissociated from I κB, it translocates to the nucleus and initiates the transcription of genes by binding to its cognate DNA motifs in the regulatory segments of genes. The active form of NF-κB induces the transcription of a variety of genes encoding proteins involved in controlling the immune and inflammatory responses, including genes encoding cytokines (*e.g.*, interleukins and tumor necrosis factor alpha), NO synthase, [cyclo-oxygenate-z]

cyclo-oxygenase-2, chemokines, growth factors, cell adhesion factors and acute phase proteins.

On page 3, please amend the paragraph beginning on line 28 as follows:

NF-κB is an early mediator of the immune and inflammatory responses, and it is involved in the control of cell proliferation and in the pathogenesis of various human diseases, including, but not limited to, rheumatoid arthritis (Beker et al., 1995, Clin. Exp. Immunol. 99: 325), ischemia (Salminen et al., 1995, Biochem. Biophys. Res. Comm. 212: 939), arteriosclerosis (Baldwin et al., 1996, Annals Rev. Immunol. 14: 649), autoimmune arthritis, asthma, septic shock, lung fibrosis, [glumerulonephritis] glomerular nephritis, and acquired immunodeficiency syndrome (AIDS). Many viruses, including human immunodeficiency virus-1 (HIV-1) and human T-cell leukemia virus type I (HTLV-1), utilize NF-κB to their [transcriptinal] transcriptional advantage during infection. For example, the transcription of HIV-1 virus RNAs by NF-κB is caused by the presence of κB-sites in the (LTR) (Long Terminal Repeats) sequences of the virus genome (Baltimore et al., 1989, Cell 58: 227-229). Therefore, the discovery of compounds that downregulate or inhibit NF-κB activation after administration to humans would be beneficial for the treatment of diseases and/or disorders associated with inappropriate or aberrant NF-κB activity.

On page 10, please amend the paragraph beginning on line 14 as follows:

Efficacy in treating or preventing viral infection may be demonstrated by detecting the ability of the cyclopentenone compound or derivative thereof to inhibit the replication of the virus, to inhibit transmission or prevent the virus from establishing itself in its host, or to prevent, ameliorate or alleviate the symptoms of disease [a] progression. The treatment is considered therapeutic if there is, for example, a reduction [is] in viral load, amelioration of one or more symptoms, or a decrease in mortality and/or morbidity following administration of the compounds of the invention.

On page 11, please amend the paragraph beginning on line 10 as follows:

It has been discovered that compounds with an α,β- unsaturated ketone ("enone") moiety are the preferred compounds of the invention. The enone moiety may be present in a ring or in an acyclic structure, for example, cyclopentenone, cyclohexenone, cycloheptone

and the like or simple acyclic α,β- unsaturated carbon chains may be used. The preferred [most] compounds of the present invention comprise compounds with a cyclopentenone ring structure. The cyclopentenone containing compounds may or may not contain long aliphatic lateral side chains similar to those present in prostaglandins or punaglandins that have a cyclopentenone ring structure (sometimes referred to as a cyclopentenone nucleus). Accordingly, the compounds may lack one or more long aliphatic lateral side chains at the 4 and/or 5 positions of the cyclopentenone ring.

On page 14, please replace the paragraph beginning on line 6 with the following paragraph:

In a preferred embodiment, therapeutic methods and pharmaceutical compositions for treating, inhibiting or preventing infectious diseases, immune disorders, cancer, ischemia, [,] arteriosclerosis and diabetes in animals, comprise 2-cyclopenten-1-one or a derivative of 2-cyclopenten-1-one.

On page 14, please amend the paragraph beginning on line 16 as follows:

In a preferred embodiment, therapeutic or pharmaceutical compositions are administered to an animal to treat, prevent or inhibit infectious diseases. Infectious diseases include diseases associated with yeast, fungal, viral and bacterial infections. Viruses causing viral infections which can be treated or prevented in accordance with this invention include, but are not limited to, retroviruses (*e.g.*, human T-cell lymphotrophic virus (HTLV) types I and II and human immunodeficiency virus (HIV)), herpes viruses (*e.g.* , herpes simplex virus (HSV) types I and II, Epstein-Barr virus, HHV6-HHV8, and cytomegalovirus), arenavirues (*e.g.*, lassa fever virus), paramyxoviruses (*e.g.*, morbillivirus virus, human respiratory syncytial virus, mumps, and pneumovirus), adenoviruses, bunyaviruses (*e.g.*, hantavirus), [cornaviruses] coronaviruses, filoviruses (*e.g.*, Ebola virus), flaviviruses (*e.g.*, hepatitis C virus (HCV), yellow fever virus, and Japanese encephalitis virus), hepadnaviruses (*e.g.*, hepatitis B viruses (HBV)), (*e.g.*, influenza viruses A, B and C), [papovaviruses] papovaviruses (*e.g.*, papillomavirues), picornaviruses (*e.g.*, rhinoviruses, enteroviruses and hepatitis A viruses), poxviruses, reoviruses (*e.g.*, [rotavirues] rotaviruses), togaviruses (*e.g.*, rubella virus), and rhabdoviruses (*e.g.*, rabies virus). Microbial pathogens causing bacterial infections include, but are not limited to, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Neisseria gonorrhoea*, *Neisseria*

meningitidis , *Corynebacterium diphtheriae*, *Clostridium botulinum*, *Clostridium perfringens*, *Clostridium tetani*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Klebsiella rhinoscleromotis*, *Staphylococcus aureus*, *Vibrio cholerae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Campylobacter* (Vibrio) *fetus*, *Campylobacter jejuni*, *Aeromonas hydrophila*, *Bacillus cereus*, *Edwardsiella tarda*, *Yersinia enterocolitica*, *Yersinia pestis*, *Yersinia pseudotuberculosis*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Salmonella typhimurium*, *Treponema pallidum*, *Treponema pertenue*, *Treponema carateneum* , *Borrelia vincentii*, *Borrelia burgdorferi*, *Leptospira icterohemorrhagiae*, *Mycobacterium tuberculosis*, *Toxoplasma gondii*, *Pneumocystis carinii*, *Francisella tularensis*, *Brucella abortus*, *Brucella suis*, *Brucella melitensis*, *Mycoplasma spp.*, *Rickettsia prowazeki*, *Rickettsia tsutsugumushi*, *Chlamydia spp.*, and *Helicobacter pylori*.

On page 17, please amend the paragraph beginning on line 30 as follows:

Efficacy in treating or preventing viral infection may be demonstrated by detecting the ability of the cyclopentenone compound to inhibit the replication of the virus, to inhibit transmission or prevent the virus from establishing itself in its host, or to prevent, ameliorate or alleviate the symptoms of disease [a] progression. The treatment is considered therapeutic if there is, for example, a reduction [is] <u>in</u> viral load, amelioration of one or more symptoms or a decrease in mortality and/or morbidity following administration of a compound of the invention.

On page 24, please amend the paragraph beginning on line 31 as follows:

In one embodiment, agents that induce one or more heat shock proteins and/or downregulate or inhibit NF-κB activity are identified in a cell-based assay system. In accordance with this embodiment, cells are contacted with a candidate compound (*e.g.*, 2-cyclopenten-1-one) or a control compound (*e.g.*, phosphate buffered saline (PBS)) and the ability of the candidate compound to induce one or more heat shock proteins and/or downregulate or inhibit NF-κB activity is determined. The level of expression of one or more heat shock proteins or the downregulation of NF-κB activity in the presence of the candidate compound is compared to the level of expression of one or more heat shock proteins or the downregulation of NF-κB activity in the absence of the candidate compound (*e.g.*, in the presence of a control compound). The candidate compound can then be

identified based on this comparison. For example, when the expression of one or more heat shock proteins is significantly greater in the presence of the candidate compound than in its absence, the candidate compound is identified as an inducer of one or more heat shock proteins. The cell, for example, can be of mammalian or human origin. The ability of the candidate compound to induce one or more heat shock proteins and/or downregulate or inhibit NF-κB activity can be determined by methods known to those of skill in the art. For example, the ability of a candidate compound to induce one or more heat shock proteins can be determined at the RNA level by Northern blot analysis or RT-PCR and at the protein level by immunoprecipitation or western blot analysis. The ability of a candidate compound to downregulate or inhibit NF-κB activity can be determined, for example, by electrophoretic shift assays, by detecting the expression of a protein known to be regulated by NF-κB, detecting the induction of a reporter gene ([]*e.g.*, an NF-κB regulatory element operably linked to a nucleic acid encoding a detectable marker, *e.g.*, luciferase, α-galactosidase or chloramphenicol acetyl transferase (CAT)), or detecting a cellular response, for example, cellular differentiation, or cell proliferation.

EXHIBIT B

A MARKED UP VERSION OF THE CLAIMS AMENDED

IN THE INSTANT AMENDMENT

FILED DECEMBER 14, 2001

IN U.S. APPLICATION SERIAL NO. 09/533,399

ATTORNEY DOCKET NO. 10167-004

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7. (amended) A method of inducing both cytoprotective and NF-κB inhibitory activities in a human comprising administering to a human in which such treatment is desired a therapeutically effective amount of a compound [with] having a cyclopentenone ring structure, [that] wherein said compound induces the expression of one or more heat shock proteins and downregulates or inhibits NF-κB activity.

12. (amended) The method of Claim 5[,] or 7 [or 10], wherein at least one of the heat shock proteins induced is HSP70.

13. (amended) The method of Claim 5, 6[,] or 7 [or 10], wherein the human has an infectious disease.

14. (amended) The method of Claim 5, 6[,] or 7 [or 10], wherein the human has an immune disorder.

15. (amended) The method of Claim 5, 6[,] or 7 [or 10], wherein the human has cancer.

16. (amended) The method of Claim 5, 6[,] or 7 [or 10], wherein the human has an inflammatory disorder.

17. (amended) The method of Claim 5, 6[,] or 7 [or 10], wherein the human has an HIV infection, an influenza virus infection, a herpesvirus infection, a hepatitis B virus infection or a hepatitis C virus infection.